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| (54) Title: ANALGESIC AND ANTI-INFLAMMATORY COMPOSITIONS COMPRISING DIPHENHYDRAMINE AND METHODS OF USING SAME | | | |
| (57) Abstract Novel pharmaceutical compositions of matter comprising analgesic/non-steroidal anti-inflammatory drugs and diphenhydramine and methods of using said compositions to elicit an enhanced analgesic and/or anti-inflammatory response in mammalian organisms in need of such treatment. | | | |

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ANALGESIC AND ANTI-INFLAMMATORY COMPOSITIONS
COMPRISING DIPHENHYDRAMINE AND METHODS OF USING SAME

BACKGROUND OF THE INVENTION

The present invention relates generally to
5 novel pharmaceutical compositions of matter comprising
diphenhydramine and one or more non-steroidal anti-
inflammatory drugs (NSAID) having analgesic and anti-
inflammatory properties, and to methods of using said
compositions to elicit an enhanced analgesic or anti-
10 inflammatory response in mammalian organisms in need of
such treatment.

Non-narcotic analgesics, most of which are
also known as non-steroidal anti-inflammatory drugs
(NSAID), are widely administered orally in the treat-
15 ment of mild to severe pain. Within this class, the
compounds vary widely in their chemical structure and
in their biological profiles as analgesics, anti-
inflammatory agents and antipyretic agents. Aspirin,
acetaminophen and phenacetin have long been among the
20 most commonly used members of this group; more
recently, however, a large number of alternative non-
narcotic agents offering a variety of advantages over
the earlier drugs have been developed. Tolerance or
addiction to these drugs is not generally a problem
25 with their continuous use in the treatment of pain or
in the treatment of acute or chronic inflammatory
states (notably, rheumatoid arthritis and osteoarthritis);
nevertheless, these drugs generally have a higher
potential for adverse side-effects at the upper limits
30 of their effective dose ranges. Moreover, above each
drug's upper limit or ceiling, administration of
additional drug does not usually increase the analgesic
or anti-inflammatory effect. Among the newer compounds

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in the non-narcotic analgesic/nonsteroidal anti-inflammatory group are compounds such as diflunisal (Dolobid[®]), zomepirac sodium (Zomax[®]), ibuprofen (Motrin[®]), naproxen (Naprosyn[®]), fenoprofen (Nalfon[®]),
5 piroxicam (Feldene[®]), flurbiprofen, mefenamic acid (Ponstel[®]) and sulindac. See also Physicians' Desk Reference, 35th edition, 1981, and The Merck Index, ninth edition, Merck & Co., Rahway, New Jersey (1976), for information on specific nonsteroidal anti-inflammatory agents. Also see, generally, Wiseman, "Pharmacological Studies with a New Class of Nonsteroidal Anti-Inflammatory Agents - The Oxicams - With Special Reference to Piroxicam (Feldene[®])", The American Journal of Medicine, February 16, 1982:2-8;
15 Foley et al, The Management of Cancer Pain, Volume II - The Rational Use of Analgesics in the Management of Cancer Pain, Hoffman-LaRoche Inc., 1981; and Cutting's Handbook of Pharmacology, sixth edition, ed. T.Z. Czaky, M.D., Appelton-Century-Crofts, New York, 1979,
20 Chapter 49: 538-550, including structural formulas for representative group members.

Diphenhydramine[2-(diphenylmethoxy)-N,N-dimethylethylamine] is also a well-known therapeutic agent in long standing use by clinicians as an
25 antihistamine. It is recognized in both the U.S.P. and N.F. as an official antihistamine of the ethanolamine (or aminoalkyl ether) type and is available as the hydrochloride salt in Benadryl[®] and various alternative sources in 50 milligram delayed action tablets, 25 and
30 50 milligram capsules, elixirs (12.5 mg/5 ml) and sterile solution for injection (10 mg/ml). Depending upon the therapeutic indication, diphenhydramine is recommended in single or divided doses of between 12.5 to 50 milligrams with a maximum daily dosage not to

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exceed 300 milligrams. The antihistaminic activity of diphenhydramine is directly attributable to its competition with histamine for cell receptor sites on effector cells although diphenhydramine also demonstrates, in addition, a number of therapeutic applications attributable to central actions unrelated to histamine antagonism. Antihistaminic indications for diphenhydramine include perennial and seasonal allergic rhinitis, vasomotor rhinitis, allergic conjunctivitis, urticaria and as adjunctive therapy for anaphylactic reactions. Central nervous system side effects (non-histaminic actions) which have been capitalized upon include prophylactic and active treatment of motion sickness and, more broadly, as an antinauseant and in the treatment of mild forms of Parkinsonism. Diphenhydramine demonstrates both stimulant and depressant effects on the central nervous system although stimulation is only occasionally seen in patients given conventional doses with accompanying restlessness, nervousness and inability to sleep. The more predominant sedative action of diphenhydramine has been beneficially capitalized upon with the usage of diphenhydramine as a somnolent when employed at the maximum 50 milligrams dose in both prescription and over-the-counter forms. In this regard, it is noted that the Food and Drug Administration announced in the November 1983 FDA Drug Bulletin (Vol. 13, No. 3) that diphenhydramine (50 mg.) may now be marketed over-the-counter as a nighttime sleep aid.

30 An early study (1958) investigated the properties of diphenhydramine as a pre-anesthetic medication. (Lear, et al., "Comparative Studies of Tranquilizers Used in Anesthesia." JAMA, 1958, 166(12): 1438-1443). The authors concluded that

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diphenhydramine, particularly when used in combination with meperidine, provides beneficial preoperative sedation with less overall depression than previously experienced with the use of routine doses or narcotics and barbiturates.

Diphenhydramine has also been investigated with varying results with respect to its potential as a weak analgesic. Diphenhydramine hydrochloride when introduced intravenously has been reported as being useful in obstetric analgesia alone and in combination with alcohol. See Cappe, B.E. et al, "Recent Advances in Obstetric Analgesia", JAMA, 1954, 154(5); 377-379. Campos et al in a comparative study found that diphenhydramine given either orally or intramuscularly could not be distinguished from placebo in patients with postoperative fractures or somatic pain. ["The Analgesic and Hypothermic Effects of Nefopam, Morphine, Aspirin, Diphenhydramine and Placebo", Journal of Clin. Pharmacology, January, 1980, pp. 42-49.]

Albal and Chandorkar studied an injectable combination analgesic consisting of analgin 375 mg, a centrally acting analgesic, diazepam 2.5 mg, and diphenhydramine 20 mg, and found relief from pain. They did not, however, study the unique contribution of diphenhydramine. [Albal, M.V., and Chandorkar, A.G. "Clinical Evaluation of Sedyn-a-Forte, an Analgesic Injection Containing Analgin, Diphenhydramine and Diazepam." Indian Journal of Ophthalmology, 1982, 30:271-273]. [Note: analgin referred to in the foregoing study is dypyrone; see The Merck Index, p. 3361, 1976.]

While diphenhydramine has been investigated with respect to its weak analgesic properties, it is also evident from the foregoing that its sedative and

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local anesthetic properties may, in part, account for its suspected potential for relieving pain. In the Lear et al, supra, study diphenhydramine at 25 to 50 milligram doses was insufficient as a preanesthetic medication and combination with meperidine (a narcotic analgesic) was proposed to optimize the potential beneficial effects of diphenhydramine as an analgesic.

Hydroxyzine, which is a minor tranquilizer with antihistaminic activity, has been evaluated as an analgesic. Beaver and Feise found that, "This study unequivocally demonstrates analgesic activity for a 100 mg dose of intramuscular hydroxyzine in the general range of that produced by 8 mg of morphine. In addition, the analgesic activity of hydroxyzine appears additive with that of morphine when the two drugs are given together." The findings of the study do not indicate synergistic activity. (Beaver, W.T. & Feise, G. "Comparison of the Analgesic Effects of Morphine, Hydroxyzine, and Their Combination in Patients with Postoperative Pain." Advances in Pain Research and Therapy, 1976, 1:553-557)

Only recently have animal studies been conducted in which the analgesic activity of diphenhydramine has been investigated. Bluhm, et al., in a study conducted on mice, found that diphenhydramine potentiates morphine, a centrally acting drug, when administered parenterally. Oral administration of drugs was not studied. (Bluhm, et al., "Potentiation of Opioid Analgesia By H₁ and H₂ Antagonists." Life Sciences, 1982, 31:1229-1232)

Diphenhydramine has not been heretofore proposed for use in combination with any of the newer nonsteroidal analgesic/anti-inflammatory agents (i.e., excluding aspirin, acetaminophen and phenacetin). In

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U.S. Patent No. 4,420,483 issued December 13, 1983, the present applicants disclose the hastening of the onset of analgesic and anti-inflammatory responses observed with several different nonsteroidal anti-inflammatory agents as well as the enhancement of the analgesic and anti-inflammatory response with such agents by the concomitant administration of caffeine as a potentiating adjuvant.

Applicants have now surprisingly found that diphenhydramine synergistically enhances the analgesic and anti-inflammatory properties of such non-steroidal anti-inflammatory drugs (NSAID).

SUMMARY OF THE INVENTION

It is, therefore, a primary object of the present invention to provide a novel pharmaceutical composition of matter for promoting an enhanced analgesic and anti-inflammatory response in a mammalian organism in need of such treatment comprising an analgesically and anti-inflammatorily effective amount of a non-steroidal anti-inflammatory drug (NSAID) in combination with diphenhydramine or a pharmaceutically acceptable salt thereof.

It is a further object of the present invention to provide methods for obtaining analgesic and anti-inflammatory responses in mammals, including humans, by the administration of preselected dosages of a non-steroidal anti-inflammatory agent, with diphenhydramine.

A still further object of the present invention is to provide a pharmaceutical composition of matter for obtaining a synergistic analgesic and anti-inflammatory response in mammals in which the

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composition comprises an analgesically and anti-inflammatory effective amount of a selected NSAID and a synergistic amount of diphenhydramine optionally in the presence of a pharmaceutically acceptable inert carrier.

Another object of the invention is to provide suitable dosage unit forms of one or more NSAID's and diphenhydramine adapted for, e.g., oral, rectal, parenteral, topical, etc., administration and useful in the treatment, management and mitigation of pain and/or inflammation.

These and other similar objects, advantages and features are accomplished according to the products, compositions and methods of the invention comprised of a non-steroidal anti-inflammatory drug or analgesic and diphenhydramine and analgesic and anti-inflammatory methods employing same.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

It has now been unexpectedly found in accordance with the present invention that the analgesic and anti-inflammatory effects observed upon the administration of a non-narcotic analgesically active non-steroidal anti-inflammatory drug (i.e., analgesic/NSAID), can be synergistically enhanced by the co-administration of diphenhydramine or a non-toxic pharmaceutically acceptable salt thereof.

As used herein, the terms "synergism" and "synergistic" are used to describe the potentiated analgesic and anti-inflammatory responses elicited by the co-administration of an analgesic NSAID and diphenhydramine (or pharmaceutically acceptable salts thereof). More specifically, these terms as used

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herein are defined in contradistinction to merely additive effects. The effects of two compounds are additive if the response to a dose of both in combination does not change when a portion of one component is removed from the mixtures and replaced by an equipotent portion of the other. If such substitution increases the response, the mixing together of the compounds is said to potentiate their effects and synergism exists.

The non-narcotic analgesics/nonsteroidal anti-inflammatory drugs for use in the compositions and methods of the present invention can be selected from the following categories:

- (1) the propionic acid derivatives;
 - (2) the acetic acid derivatives;
 - (3) the fenamic acid derivatives;
 - (4) the biphenylcarboxylic acid derivatives;
- and
- (5) the oxicams.

The term "selected NSAID" as used herein is intended to mean any non-narcotic analgesic/nonsteroidal anti-inflammatory compound falling within one of the five structural categories above but excluding aspirin, acetaminophen and phenacetin.

While some of these compounds are primarily used at the present time as anti-inflammatory agents and others are primarily used as analgesics, in fact all of the contemplated compounds have both analgesic and anti-inflammatory activity and can be used at appropriate dosage levels for either purpose in the compositions and methods of the present invention. The compounds in groups (1) through (4) typically contain a carboxylic acid function; however, those acids are sometimes administered in the form of their pharmaceutically acceptable acid addition or alkali metal salts, e.g., sodium salts.

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The propionic acid derivatives for use herein include, but are not limited to, ibuprofen, naproxen, benoxaprofen, flurbiprofen, fenoprofen, fenbufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, tiaprofenic acid, fluprofen and bucloxic acid. Structurally related propionic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group. Presently preferred members of the propionic acid group include ibuprofen, naproxen, flurbiprofen, fenoprofen, ketoprofen and fenbufen.

Thus, "propionic acid derivatives" as defined herein are non-narcotic analgesics/nonsteroidal anti-inflammatory drugs having a free $-\text{CH}(\text{CH}_3)\text{COOH}$ or $-\text{CH}_2\text{CH}_2\text{COOH}$ group (which optionally can be in the form of a pharmaceutically acceptable salt group, e.g. $-\text{CH}(\text{CH}_3)\text{COO}^-\text{Na}^+$ or $-\text{CH}_2\text{CH}_2\text{COO}^-\text{Na}^+$), typically attached directly or via a carbonyl function to a ring system, preferably to an aromatic ring system.

The acetic acid derivatives for use herein include, but are not limited to, indomethacin, sulindac, tolmetin, zomepirac, diclofenac, fenclofenac, alclofenac, ibufenac, isoxepac, furofenac, tiopinac, zidometacin, acetaminophen, fentiazac, clidanac and oxpinac. Structurally related acetic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group. Presently preferred members of the acetic acid group include tolmetin sodium, zomepirac sodium, sulindac and indomethacin.

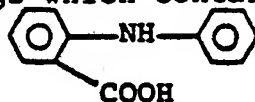
Thus, "acetic acid derivatives" as defined herein are non-narcotic analgesics/nonsteroidal anti-inflammatory drugs having a free $-\text{CH}_2\text{COOH}$ group (which

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optionally can be in the form of a pharmaceutically acceptable salt group, e.g., $-\text{CH}_2\text{COO}^-\text{Na}^+$), typically attached directly to a ring system, preferably to an aromatic or heteroaromatic ring system.

5 The fenamic acid derivatives for use herein include, but are not limited to, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid and tolfenamic acid. Structurally related fenamic acid derivatives having similar analgesic and anti-
10 inflammatory properties are also intended to be encompassed by this group. Presently preferred members of the fenamic acid group include mefenamic acid and meclofenamate sodium (meclofenamic acid, sodium salt).

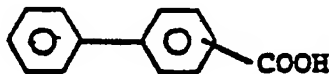
 Thus, "fenamic acid derivative" as defined
15 herein are non-narcotic analgesics/nonsteroidal anti-inflammatory drugs which contain the basic structure



which can bear a variety of substituents and in which the free $-\text{COOH}$ group can be in the form of a pharmaceutically acceptable salt group, e.g., $-\text{COO}^-\text{Na}^+$.
20

 The biphenylcarboxylic acid derivatives for use herein include, but are not limited to, diflunisal and flufenisal. Structurally related biphenylcarboxylic acid derivatives having similar analgesic and
25 anti-inflammatory properties are also intended to be encompassed by this group. Preferred members of this group are diflunisal and flufenisal.

 Thus, "biphenylcarboxylic acid derivative" as defined herein are non-narcotic analgesics/nonsteroidal
30 anti-inflammatory drugs which contain the basic structure

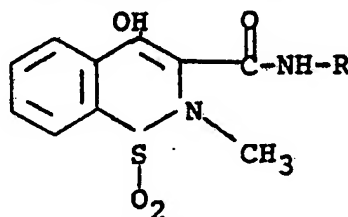


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which can bear a variety of substituents and in which the free -COOH group can be in the form of a pharmaceutically acceptable salt group, e.g. -COO⁻Na⁺.

The oxicams for use herein include, but are not limited to, piroxicam, sudoxicam, isoxicam and CP-14, 304. Structurally related oxicams having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group. A preferred member of this group is piroxicam.

Thus, "oxicams" as defined herein are non-narcotic analgesics/nonsteroidal anti-inflammatory drugs which have the general formula



wherein R is an aryl or heteroaryl ring system.

The precise amount of non-narcotic analgesic/non-steroidal anti-inflammatory drug for use in the present compositions will vary depending, for example, on the specific drug chosen, the dosage form thereof, i.e., standard versus sustained release, the condition for which the drug is administered and the size and kind of the mammal.

For humans, typical effective analgesic/anti-inflammatory amounts of presently preferred NSAIDs for use in unit dose compositions of the invention are about 125 to 500 mg diflunisal, about 25 to 100 mg zomepirac sodium, about 50 to 400 mg ibuprofen, most preferably 100-400 mg, about 125 to 500 mg naproxen, about 25 to 50 mg flurbiprofen, and about 50 to 200 mg fenoprofen, about 10 to 20 mg piroxicam, about 125 to

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250 mg mefenamic acid, about 100 to 400 mg fenbufen or about 25 to 50 mg ketoprofen; however, greater or lesser amounts can be employed if desired.

For example, in one preferred embodiment of this invention, the desired therapeutic response for ibuprofen therapy in mild to moderate pain is generally observed at 200 to 600 milligrams of ibuprofen every 4 to 6 hours as necessary up to about 2400 milligrams total daily dose. Consistent with the synergistic results achieved with the ibuprofen/diphenhydramine compositions and methods of the present invention, the desired analgesic and/or anti-inflammatory response can be achieved upon the administration of ibuprofen and diphenhydramine wherein the ibuprofen component can be administered at reduced levels of between about 50 to 400 milligrams of ibuprofen and, most preferably, 100 to 400 milligrams. Alternatively, the usual dosage regimen for ibuprofen may be followed when the composition of the present invention additionally comprising diphenhydramine is employed whereby the levels of analgesia and anti-inflammatory results are enhanced.

The amount of diphenhydramine present in the compositions according to the present invention ranges between about 12.5 to 50 milligrams and, preferably, between about 25 to 50 milligrams.

In any event, the amounts of NSAID and diphenhydramine to be administered in a total daily dose should not exceed the generally recognized as safe limits established for the particular NSAID and diphenhydramine when administered alone for their respective usual therapeutic indications.

In the compositions and methods of the invention, an NSAID and diphenhydramine may be co-administered in the same composition or concomitantly administered separately.

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In accordance with the practices of the present invention, the NSAID/diphenhydramine compositions may be administered in admixture with suitable pharmaceutical diluents, carriers or other excipients (collectively referred to as "carrier" materials) suitably selected with respect to the intended route of administration and conventional pharmaceutical practices. For instance, for oral administration in the form of tablets or capsules, the active drug components may be combined with any oral non-toxic pharmaceutically acceptable inert carrier such as lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated in the mixture. Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethyl-cellulose, polyethylene glycol and waxes. Among the lubricants there may be mentioned for use in these dosage forms, boric acid, sodium benzoate, sodium acetate, sodium chloride, etc. Disintegrators include, without limitation, starch, methylcellulose, agar, bentonite, guar gum, etc. Sweetening and flavoring agents and preservatives can also be included where appropriate. Similarly, injectable dosage units may be utilized to accomplish intravenous, intramuscular or subcutaneous administration and, for such parenteral administration, suitable sterile aqueous or non-aqueous solutions or suspensions, optionally containing appropriate solutes to effectuate isotonicity, will be employed.

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Moreover, in accordance with another preferred embodiment of the present invention, where therapeutic indications warrant, such as in the case where the level of pain and inflammation associated with the disorder may interfere with normal sleep latency and maintenance dosage regimens may be contemplated, the NSAID/diphenhydramine compositions of the invention may be formulated for administration at bedtime as an analgesically and anti-inflammatorily effective nighttime sleep aid. Accordingly, the NSAID and diphenhydramine components of the composition may be formulated in dosage unit form to provide a dose of diphenhydramine (compared to the amount necessary to promote the desired synergistic response) to take advantage of the sleep-inducing side effect of diphenhydramine.

In another preferred embodiment, the advantageous analgesic and anti-inflammatory compositions of the invention may be formulated in sustained release form to provide the rate controlled release of either or both of the components to optimize analgesic and anti-inflammatory response while minimizing undesirable side effects in, for example, patients unusually sensitive to either or both of the active drugs. Suitable dosage forms for sustained release include layered tablets containing layers of varying disintegration rates or controlled release polymeric matrices impregnated with the active components and shaped in tablet form or capsules containing such impregnated or encapsulated porous polymeric matrices. Thus, with respect to such layered tablets, one layer may contain an initial dosing amount of, for example, ibuprofen, of 400 milligrams and 25 milligrams of diphenhydramine, whereas two or more further layers

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may contain, for instance, 100 milligrams of ibuprofen and 15 to 25 milligrams of diphenhydramine to be released serially every 4 to 6 hours consistent with the normal dosage schedule. Another advantage afforded
5 the analgesic and anti-inflammatory compositions of the present invention by the inclusion of the diphenhydramine component is that gastro-intestinal disturbances, which are the most frequent adverse reactions reported for non-steroidal anti-inflammatory
10 drugs, including complaints involving abdominal distress, epigastric pain, indigestion, nausea and vomiting may often be minimized or, at least, reduced. The foregoing advantage is both a function of the synergism exhibited by the NSAID/diphenhydramine
15 composition which allows for the use of the NSAID component in quantities substantially less than dosages presently considered necessary as an analgesic or anti-inflammatory agent in humans, which lower doses result in lowering the incidence or severity of undesirable
20 side effects, as well as the presence of diphenhydramine contributing valuable antinauseant and antiemetic properties to the composition.

In patients particularly susceptible to the tendency of either the NSAID or diphenhydramine to
25 promote drowsiness or, in the extreme, sedation and, otherwise, in ambulatory patients where drowsiness and/or sedation may represent untoward side effects, the compositions of the present invention may further include caffeine to counteract drowsiness symptoms and
30 to further take advantage of the potentiated analgesic and anti-inflammatory response effectuated by the addition of caffeine as disclosed in applicants U.S. Patent No. 4,420,483.

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Example 1 - Pharmacologic Test
for Synergism - Ibuprofen/Diphenhydramine.

The unexpected synergistic analgesic effect of the addition of diphenhydramine to ibuprofen is evidenced by tests conducted on mice. Blue Spruce Farm male mice weighing 18-28 grams at the time of testing are used throughout. All mice are dosed orally by gavage with ibuprofen and/or diphenhydramine. The formulation of each test article is a solution or suspension in 0.25% methylcellulose manufactured by Fisher Scientific Company. A dosing volume of 10 ml/mg is used. All doses are coded and the test is performed under a code not known to the observer. Doses are based upon the weights of the animal taken prior to dosing.

METHOD

A phenylquinone writhing assay in mice was conducted over a four day period to test for synergism of the analgesic activity of ibuprofen and diphenhydramine.

The assay consists of phenyl-p-benzoquinone (PPQ) introduced in mice thirty minutes post dose of the test treatment(s). The PPQ is prepared as a .02% aqueous solution in 5 ml ethyl alcohol q.s. to 100 ml with distilled water and is administered intraperitoneally at .25 ml/mouse. The mice are injected with the PPQ solution and are placed in individual plastic squares 4"x4"x5" deep and observed for a ten minute period post treatment dose for exhibition of the writhing syndrome. Complete blocking of the writhing syndrome for the ten minute observation period in any

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one mouse is considered a positive response for that mouse. Conversely, if the mouse definitely writhes at least once, it is considered to be not protected from the PPQ.

5 Three hundred twenty-eight mice were randomly assigned to 40 groups. Two groups of ten mice per series were assigned to a control group (10 prior to the administration of the test treatments and 10 post administration) to verify the ability of the solutions
10 to produce the writhing response.

 The purpose of the assay on the first day is to estimate the ED_{50} (effective dose in 50% of treated mice) of ibuprofen alone and of diphenhydramine alone, and to estimate the relative potency, ρ , of ibuprofen to
15 diphenhydramine, determined as the ratio of the ED_{50} of ibuprofen to the ED_{50} of diphenhydramine. Eight mice per group are dosed orally (via intubation) with 2, 5, 10 and 20 mg/kg of ibuprofen and 5, 10, 20 and 50 mg/kg of diphenhydramine. Table 1 shows the number of mice
20 protected from writhing activity for each dose of ibuprofen and diphenhydramine. The method of Finney ["Statistical Method of Biological Assay", McMillan Pub., 3rd Edition, 1978] is used to estimate the ED_{50} 's of ibuprofen alone and diphenhydramine alone.

25 On the second day eight combination doses were studied. The doses were chosen based upon the ED_{50} 's established in the preceding day's experiment, which, under the assumption of additivity, would provide protection for 50% of the mice. These doses
30 were tested in order to observe those ratio(s) of the combination drugs that would yield a synergistic effect. Combinations for which five or more mice exhibit blockage of writhing are candidates for further study. The doses of the constituent drugs in mg/kg for

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the eight groups were for ibuprofen (I) and diphenhydramine (D) respectively, [abbreviated as (I,D)]:
(22,4), (19,8), (16,12), (14,6), (11,20), (9,24),
(6,28), (4,32). Table 2 shows for each of these combination doses, the number of mice protected from writhing activity.

On the third and fourth days the four specific fixed ratios that achieved 5 or more protected mice were studied in more detail, i.e., the first combination treatment used a ratio of ibuprofen to diphenhydramine of 19:8 and the doses of the constituent drugs in mg/kg that were studied were (8,3), (12,5), (16,7) and (28,12). The second combination treatment used a ratio of doses of ibuprofen to diphenhydramine of 6:28 and the doses of the constituent drugs in mg/kg that were studied were (3,14), (4.5,21) and (9,42). The third combination treatment used a ratio of doses of ibuprofen to diphenhydramine of 9:24 and the doses of the constituent drugs in mg/kg that were studied were (3,8), (6,16), (12,32) and (15,40). The fourth combination treatment used a ratio of doses of ibuprofen to diphenhydramine of 4:32 and the doses of the constituent drugs in mg/kg that were studied were (3,24), (3.5,28) (4.5,36) and (5,40).

Under the assumption of additivity each dose of each combination is equivalent to a dose of ibuprofen, based on the relative potency (p) of diphenhydramine to ibuprofen obtained from the experiment on the first day. Thus, for example, in the dose ratio 19:8 the combination of 28 mg/kg of ibuprofen and 12 mg/kg of diphenhydramine is, under the assumption of additivity, equivalent to $(28+12p)$ mg/kg of ibuprofen. Table 3 shows for each dose of each of the combination doses tested the number of mice observed to

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be protected and the ibuprofen equivalent dose. For each of the four combination ratios, ED₅₀'s were estimated based on the observed number of mice protected at each ibuprofen equivalent dose using the method of Finney. Table 4 displays the estimated ED₅₀'s for each ratio.

RESULTS

The surprising synergistic effects of combining ibuprofen with diphenhydramine can be seen from the results of Tables 3 and 4 and Figure 1. Figure 1 summarizes all of the findings by depicting the ED₅₀'s obtained for each treatment alone, the ED₅₀ line if the treatments were additive, the number of mice/protected from writhing for each treatment studied and the estimated ED₅₀'s for each combination ratio.

The ED₅₀ of ibuprofen alone is estimated to be 24 mg/kg and for diphenhydramine to be 38 mg/kg. The relative potency of diphenhydramine to ibuprofen is 24/38. Among the 8 ratios tested on the second day, synergism appears to be present for four ratios, and these ratios were further investigated on days 3 and 4. The ED₅₀'s were found to be for the dosage ratio of 19:8, 23 mg/kg of ibuprofen, for the dosage ratio 6:28, 19 mg/kg of ibuprofen, for the dosage ratio 9:24, 18 mg/kg of ibuprofen, and for the dosage ratio 4:32, 23 mg/kg of ibuprofen. Two of these ED₅₀'s are substantially less than 24 mg/kg of ibuprofen which is the ED₅₀ that would be expected if the effects were additive. This represents a 25% reduction of the amount of ibuprofen that is required to obtain the effect in 50% of the animals. The graph in Figure 1 indicates that many other dose ratios as well would produce an unexpected synergistic effect.

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Table 1

| NUMBER OF MICE PROTECTED AT TESTED DOSE LEVELS OF IBUPROFEN AND DIPHENHYDRAMINE | | | |
|---|--|---|---|
| <u>Dose of Ibuprofen</u> <u>mg/kg</u> | <u>Dose of Diphenhydramine</u> <u>mg/kg</u> | <u>Number of Mice</u> <u>Protected</u> | <u>Number of Mice</u> <u>Not Protected</u> |
| 2 | - | 0 | 0 |
| 5 | - | 0 | 0 |
| 10 | - | 1 | 7 |
| 20 | - | 3 | 5 |
| - | 5 | 1 | 7 |
| - | 10 | 2 | 6 |
| - | 20 | 3 | 5 |
| - | 40 | 4 | 4 |

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Table 2

NUMBER OF MICE PROTECTED AT TESTED DOSES* OF THE COMBINATION
OF IBUPROFEN AND DIPHENHYDRAMINE

| <u>Dose of Ibuprofen</u> <u>mg/kg</u> | <u>Dose of Diphenhydramine</u> <u>mg/kg</u> | <u>Number of Mice</u> <u>Protected</u> | <u>Number of Mice</u> <u>Not Protected</u> |
|--|--|---|---|
| 22 | 4 | 4 | 4 |
| 19 | 8 | 5 | 3 |
| 16 | 12 | 3 | 5 |
| 14 | 16 | 4 | 4 |
| 11 | 20 | 4 | 4 |
| 9 | 24 | 5 | 3 |
| 6 | 28 | 5 | 3 |
| 4 | 32 | 5 | 3 |

* Doses were chosen based upon ED₅₀'s of ibuprofen and diphenhydramine which under the assumption of additivity would provide protection for 50% of the mice.

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Table 3

NUMBER OF MICE PROTECTED AT TESTED DOSE LEVELS OF FOUR DIFFERENT RATIOS
OF DOSES OF IBUPROFEN TO DIPHENHYDRAMINE

| <u>Combination Dose Ratio</u> | <u>Dose of Ibuprofen mg/kg</u> | <u>Dose of Diphenhydramine mg/kg</u> | <u>Ibuprofen Equivalent Dose Under Assumption of Additivity mg/kg</u> | <u>Number of Mice Protected</u> | <u>Number of Mice Not Protected</u> |
|-----------------------------------|--|--|---|-------------------------------------|---|
| 19:0 | 0 | 3 | 9.9 | 1 | 7 |
| | 12 | 5 | 15.2 | 3 | 5 |
| | 16 | 7 | 20.4 | 2 | 6 |
| | 20 | 12 | 35.6 | 6 | 2 |
| 9:24 | 3 | 8 | 0.0 | 2 | 3 |
| | 6 | 16 | 16.1 | 2 | 6 |
| | 12 | 32 | 32.2 | 6 | 2 |
| | 15 | 40 | 40.2 | 0 | 0 |
| 6:20 | 3 | 14 | 11.0 | 2 | 6 |
| | 4.5 | 21 | 17.7 | 3 | 5 |
| | 9 | 42 | 35.5 | 7 | 1 |
| 4:32 | 3 | 24 | 18.1 | 2 | 6 |
| | 3.5 | 28 | 21.1 | 3 | 5 |
| | 4.5 | 36 | 27.2 | 6 | 2 |
| | 5 | 40 | 30.2 | 6 | 2 |

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Table 4

ED₅₀'s OF COMBINATION TREATMENTS IN IBUPROFEN EQUIVALENT DOSESTested Combination Dose Ratios
of Ibuprofen to DiphenhydramineIbuprofen Equivalent
ED₅₀ mg/kg

| <u>I</u> | <u>D</u> | <u>I</u> |
|----------|----------|----------|
| 100 | 0 | 24 |
| 19 | 8 | 23 |
| 9 | 24 | 18* |
| 6 | 28 | 19* |
| 4 | 32 | 23 |
| 0 | 100 | 24 |

* ED₅₀'s substantially less than 24 mg/kg, the dose that would be expected were the effects additive.

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While the invention has been described and illustrated with reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions
5 can be made therein without departing from the spirit of the invention. For example, effective dosages other than the preferred ranges set forth hereinabove may be applicable as a consequence of variations in the responsiveness of the mammal treated, severity of pain
10 or inflammation, dosage related adverse effects, if any, observed and analogous considerations. Likewise, the specific pharmacological responses observed may vary depending upon the particular relative amounts of active components employed or whether same are used in
15 combination with suitable pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in results are contemplated in accordance with the objects and practices of the present inven-
20 tion. It is intended, therefore, that the invention be limited only by the scope of the claims which follow.

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CLAIMS

1. A pharmaceutical composition of matter
for promoting an enhanced analgesic and anti-
inflammatory response in a mammalian organism, said
5 composition comprising an analgesically and anti-
inflammatorily effective amount of a nonsteroidal
anti-inflammatory drug selected from the group
consisting of propionic acid derivatives, acetic acid
derivatives, fenamic acid derivatives, biphenyl-
10 carboxylic acid derivatives and oxicams and an amount
of diphenhydramine sufficient to synergistically
enhance said analgesic and anti-inflammatory response.
2. A composition according to Claim 1,
wherein the nonsteroidal anti-inflammatory drug is a
15 propionic acid derivative.
3. A composition according to Claim 1,
wherein the nonsteroidal anti-inflammatory drug is an
acetic acid derivative.
4. A composition according to Claim 1,
20 wherein the nonsteroidal anti-inflammatory drug is a
fenamic acid derivative.
5. A composition according to Claim 1,
wherein the nonsteroidal anti-inflammatory drug is a
biphenyl-carboxylic acid derivative.
- 25 6. A composition according to Claim 1,
wherein the nonsteroidal anti-inflammatory drug is an
oxicam.

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7. A composition according to Claim 2,
wherein the propionic acid derivative is ibuprofen,
naproxen, benoxaprofen, flurbiprofen, fenoprofen,
fenbufen, ketoprofen, indoprofen, piroprofen, carprofen,
5 oxaproxin, pranoprofen, miroprofen, tioxaprofen,
suprofen, aluminoprofen, tiaprofenic acid, fluprofen or
bucloxic acid.

8. A composition according to Claim 2,
wherein the propionic acid derivative is ibuprofen.

10 9. A composition according to Claim 3,
wherein the acetic acid derivative is indomethacin,
sulindac, tolmetin, zomepirac, diclofenac, fenclofenac,
alclofenac, ibufenac, isoxepac, furofenac, tiopinac,
zidometacin, acetmetacin, fentiazac, clidanac or
15 oxepinac.

10. A composition according to Claim 3,
wherein the acetic acid derivative is zomepirac
sodium.

11. A composition according to Claim 4,
20 wherein the fenamic acid derivative is mefenamic acid,
meclofenamic acid, flufenamic acid, niflumic acid
ortolfenamic acid.

12. A composition according to Claim 4,
wherein the fenamic acid derivative is mefenamic acid.

13. A composition according to Claim 5,
25 wherein the biphenylcarboxylic acid is diflunisal or
flufenisal.

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14. A composition according to Claim 5, wherein the biphenylcarboxylic acid is diflunisal.

15. A composition according to Claim 6, wherein the oxcam is piroxicam.

5 16. A pharmaceutical composition according to Claim 1, further comprising a nontoxic pharmaceutically acceptable inert carrier.

10 17. A pharmaceutical composition according to Claims 1 or 8, comprising from about 50 to 400 mg ibuprofen.

18. A pharmaceutical composition according to Claim 1, comprising from about 12.5 to 50 mg. diphenhydramine.

15 19. A pharmaceutical composition according to Claim 1, wherein said diphenhydramine is present as the pharmaceutically acceptable salt thereof.

20 20. A pharmaceutical composition according to Claim 5, wherein said pharmaceutically acceptable salt is the hydrochloride.

20 21. A pharmaceutical composition according to Claims 1 or 8, comprising from about 100 to 400 mg ibuprofen and from about 25 to 50 mg diphenhydramine.

25 22. A pharmaceutical composition according to Claims 1 or 2, said composition being adapted for oral administration.

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23. A pharmaceutical composition according to Claim 22, said composition being formulated as a tablet, capsule or elixir.

24. A pharmaceutical composition according to Claim 1, said composition being adapted for oral administration in sustained release form.

25. A pharmaceutical composition according to Claims 1 or 2, said composition being adapted for parenteral administration.

26. A pharmaceutical composition according to Claim 25, said composition being formulated for intramuscular administration.

27. A pharmaceutical composition of matter for promoting an enhanced analgesic and anti-inflammatory response in a mammalian organism, said composition comprising an analgesically and anti-inflammatorily effective amount of a nonsteroidal anti-inflammatory drug selected from the group consisting of about 100mg to 400 mg of propionic acid derivatives, about 25 mg to 200 mg of acetic acid derivatives, about 125 mg to 250 mg of fenamic acid derivatives, about 125 mg to 500 mg of biphenyl-carboxylic acid derivatives and about 10 mg to 20 mg of oxycam and an amount of diphenhydramine sufficient to synergistically enhance said analgesic and anti-inflammatory response.

28. A method for promoting an enhanced analgesic and anti-inflammatory response in a mammalian organism in need of such treatment, comprising

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administering to such organism an analgesically and anti-inflammatorily effective amount of a non-steroidal anti-inflammatory drug selected from the group consisting of propionic acid derivatives, acetic acid
5 derivatives, fenamic acid derivatives, biphenyl-carboxylic acid derivatives and oxicams and an amount of diphenhydramine sufficient to synergistically enhance said analgesic and anti-inflammatory response.

29. A method according to Claim 28, wherein
10 the non-steroidal anti-inflammatory drug is a propionic acid derivative.

30. A method according to Claim 28, wherein the non-steroidal anti-inflammatory drug is an acetic acid derivative.

31. A method according to Claim 28, wherein
15 the non-steroidal anti-inflammatory drug is a fenamic acid derivative.

32. A method according to Claim 28, wherein
20 the non-steroidal anti-inflammatory drug is a biphenyl carboxylic acid derivative.

33. A method according to Claim 28, wherein the non-steroidal anti-inflammatory drug is an oxicam.

34. A method according to Claim 28, wherein
25 the propionic acid derivative is ibuprofen, naproxen, benoxaprofen, flurbiprofen, fenoprofen, fenbufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaproxin, pranoprofen, miroprofen, tioxaprofen, suprofen, aluminoprofen, tiaprofenic acid, fluprofen or bucloxic acid.

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35. A method according to Claim 28, wherein the propionic acid derivative is ibuprofen.

36. A method according to Claim 28, wherein the acetic acid derivative is indomethacin, sulindac,
5 tolmetin, zomepirac, diclofenac, fenclofenac, alclofenac, ibufenac, isoxepac, furofenac, tiopinac, zidometacin, acetmetacin, fentiazac, clidanac or oxepinac.

37. A method according to Claim 28, wherein
10 the acetic acid derivative is zomepirac sodium.

38. A method according to Claim 28, wherein the fenamic acid derivative is mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid
ortolfenamic acid.

39. A method according to Claim 28, wherein
15 the fenamic acid derivative is mefenamic acid.

40. A method according to Claim 28, wherein the biphenylcarboxylic acid is diflunisal or flufenisal.

41. A method according to Claim 28, wherein
20 the biphenylcarboxylic acid is diflunisal.

42. A method according to Claim 28, wherein the oxicam is piroxicam.

43. A method according to Claim 29,
25 comprising from about 50 to 400 mg ibuprofen.

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44. A method according to Claim 43, comprising from about 100 to 400 mg ibuprofen.

45. A method according to Claim 28, comprising from about 12.5 to 50 mg diphenhydramine.

5 46. A method according to Claim 45, comprising from about 25 to 50 mg diphenhydramine.

47. A method according to Claim 28, wherein said composition is administered orally.

10 48. A method according to Claim 47, wherein said composition is administered daily in divided doses comprising from about 100 to 400 mg ibuprofen and 25 to 50 mg diphenhydramine.

15 49. A method for promoting an enhanced analgesic and anti-inflammatory response in a mammalian organism in need of such treatment, comprising administering to such organism an analgesically and anti-inflammatorily effective amount of the composition according to Claim 27.

20 50. A method according to Claim 13, wherein said composition is administered orally at bedtime as an analgesically and anti-inflammatorily effective nighttime sleep aid.

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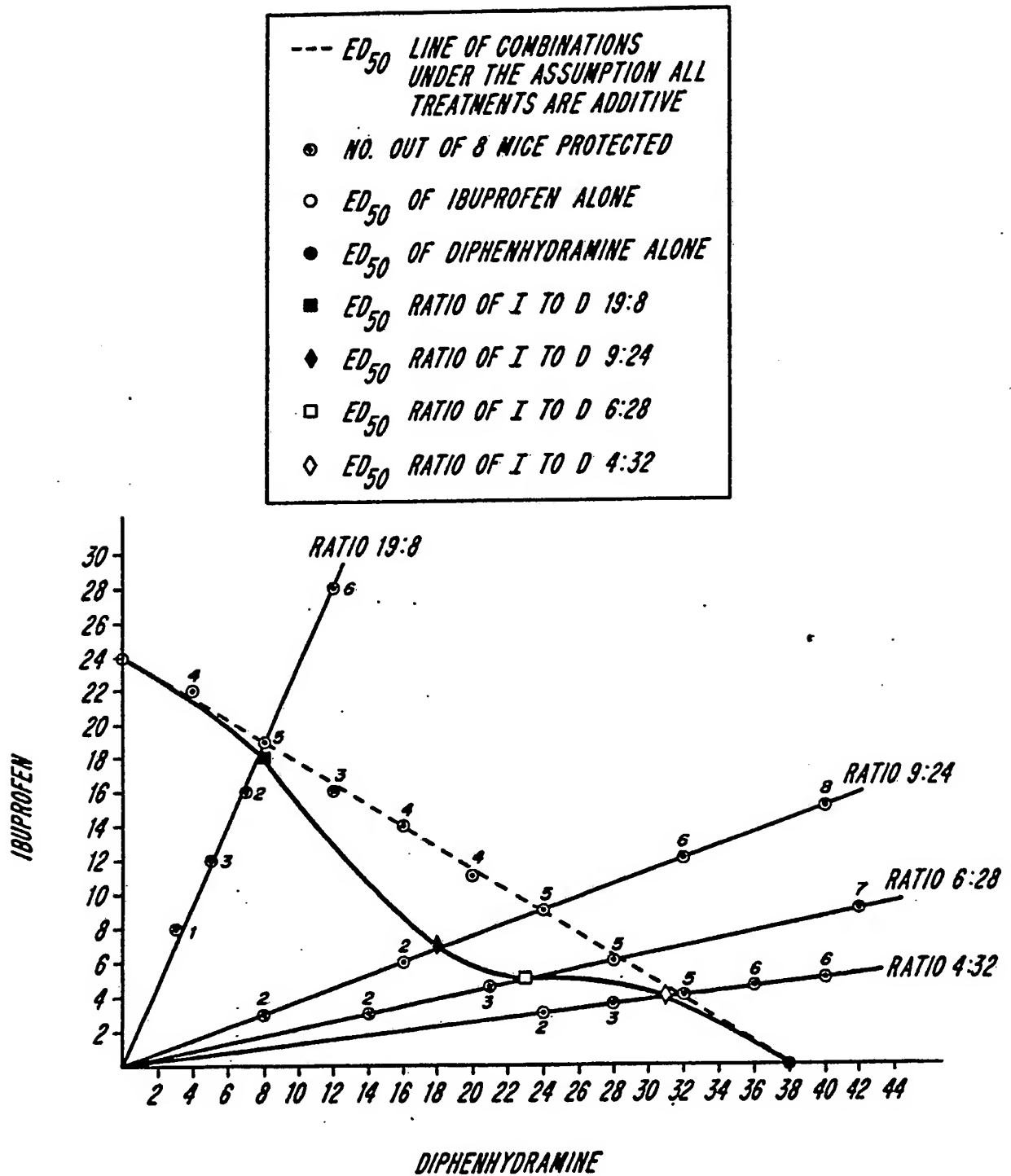


FIG. 1

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 85/00195

| I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC ⁴ : A 61 K 45/06; A 61 K 31/19 // (A 61 K 31/19; 31/135) | | | | | | | | | | | | | | | | | |
|---|--|-------------------------------------|---|--|-------------------------------------|-------------|---|---------------------------------|------------------------|--|------|---|---|------|------|--|------|
| II. FIELDS SEARCHED <div style="text-align: center;">Minimum Documentation Searched ⁷</div> <table style="width: 100%; border: none;"> <tr> <td style="width: 30%; border-bottom: 1px solid black;">Classification System</td> <td style="border-bottom: 1px solid black;">Classification Symbols</td> </tr> <tr> <td style="border: 1px solid black; padding: 5px;">IPC⁴</td> <td style="border: 1px solid black; padding: 5px;">A 61 K</td> </tr> </table> <div style="text-align: center; font-size: small; margin-top: 5px;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸</div> | | | Classification System | Classification Symbols | IPC ⁴ | A 61 K | | | | | | | | | | | |
| Classification System | Classification Symbols | | | | | | | | | | | | | | | | |
| IPC ⁴ | A 61 K | | | | | | | | | | | | | | | | |
| III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹ <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%; text-align: left; font-size: small;">Category ¹⁰</th> <th style="width: 70%; text-align: left; font-size: small;">Citation of Document, ¹¹ with Indication, where appropriate, of the relevant passages ¹²</th> <th style="width: 20%; text-align: left; font-size: small;">Relevant to Claim No. ¹³</th> </tr> </thead> <tbody> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td>Unlisted Drugs, vol. 20, no. 11, November 1968 (Chatham, New Jersey, US) page 167e "Infacete" --</td> <td style="vertical-align: top;">1-27</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td>Dictionnaire Vidal, 1961, O.V.P. (Paris, FR) page 51: "Allerga-Aspirine" --</td> <td style="vertical-align: top;">1-27</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td>Rote Liste, 1961, Edition Cantor (Aulendorf/Württ., DE) page 841 "Schwöpyrin" --</td> <td style="vertical-align: top;">1-27</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">P, X</td> <td>Chemical Abstracts, vol. 101, no. 23, 3 December 1984 (Columbus, Ohio, US) D.L. Traber: "Ibuprofen and diphenhydramine reduce the lung lesion of endotoxemia in sheep", see page 39, left-hand column, abstract no. 204101x, & J. Trauma 1984, 24(9), 835-40</td> <td style="vertical-align: top;">1-27</td> </tr> </tbody> </table> | | | Category ¹⁰ | Citation of Document, ¹¹ with Indication, where appropriate, of the relevant passages ¹² | Relevant to Claim No. ¹³ | A | Unlisted Drugs, vol. 20, no. 11, November 1968 (Chatham, New Jersey, US) page 167e "Infacete" -- | 1-27 | A | Dictionnaire Vidal, 1961, O.V.P. (Paris, FR) page 51: "Allerga-Aspirine" -- | 1-27 | A | Rote Liste, 1961, Edition Cantor (Aulendorf/Württ., DE) page 841 "Schwöpyrin" -- | 1-27 | P, X | Chemical Abstracts, vol. 101, no. 23, 3 December 1984 (Columbus, Ohio, US) D.L. Traber: "Ibuprofen and diphenhydramine reduce the lung lesion of endotoxemia in sheep", see page 39, left-hand column, abstract no. 204101x, & J. Trauma 1984, 24(9), 835-40 | 1-27 |
| Category ¹⁰ | Citation of Document, ¹¹ with Indication, where appropriate, of the relevant passages ¹² | Relevant to Claim No. ¹³ | | | | | | | | | | | | | | | |
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| A | Rote Liste, 1961, Edition Cantor (Aulendorf/Württ., DE) page 841 "Schwöpyrin" -- | 1-27 | | | | | | | | | | | | | | | |
| P, X | Chemical Abstracts, vol. 101, no. 23, 3 December 1984 (Columbus, Ohio, US) D.L. Traber: "Ibuprofen and diphenhydramine reduce the lung lesion of endotoxemia in sheep", see page 39, left-hand column, abstract no. 204101x, & J. Trauma 1984, 24(9), 835-40 | 1-27 | | | | | | | | | | | | | | | |
| <div style="display: flex; justify-content: space-between; font-size: x-small;"> <div style="width: 45%;"> <p>* Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"A" document member of the same patent family</p> </div> </div> | | | | | | | | | | | | | | | | | |
| IV. CERTIFICATION <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border-bottom: 1px solid black;">Date of the Actual Completion of the International Search</td> <td style="width: 50%; border-bottom: 1px solid black;">Date of Mailing of this International Search Report</td> </tr> <tr> <td style="border-bottom: 1px solid black; text-align: center;">26th April 1985</td> <td style="border-bottom: 1px solid black; text-align: center;">31 MAI 1985</td> </tr> <tr> <td style="border-bottom: 1px solid black;">International Searching Authority</td> <td style="border-bottom: 1px solid black;">Signature of Authorized Officer</td> </tr> <tr> <td style="text-align: center;">EUROPEAN PATENT OFFICE</td> <td style="text-align: right;">G.L.M. Kruidenberg</td> </tr> </table> | | | Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report | 26th April 1985 | 31 MAI 1985 | International Searching Authority | Signature of Authorized Officer | EUROPEAN PATENT OFFICE | G.L.M. Kruidenberg | | | | | | | |
| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report | | | | | | | | | | | | | | | | |
| 26th April 1985 | 31 MAI 1985 | | | | | | | | | | | | | | | | |
| International Searching Authority | Signature of Authorized Officer | | | | | | | | | | | | | | | | |
| EUROPEAN PATENT OFFICE | G.L.M. Kruidenberg | | | | | | | | | | | | | | | | |

| III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET) | | |
|--|---|----------------------|
| Category * | Citation of Document, with indication, where appropriate, of the relevant passages | Relevant to Claim No |
| A | <p>US, A, 4420483 (ABRAHAM SUNSHINE) 13 December 1983 (cited in the application)</p> <p>-----</p> | 1-27 |

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers ^{o)} because they relate to subject matter not required to be searched by this Authority, namely:

o) 28-50. See Rule 39.1:iv : Methods for treatment of the human or animal body by surgery or therapy as well as diagnostic methods

2. ☐ Claim numbers because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/US 8500195 (SA 8863)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 15/05/85

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|--|---------------------|----------------------------|---------------------|
| US-A- 4420483 | 13/12/83 | BE-A- 897355 | 14/11/83 |
| | | FR-A- 2530468 | 27/01/84 |
| | | WO-A- 8400487 | 16/02/84 |
| | | AU-A- 1828783 | 23/02/84 |
| | | SE-A- 8401537 | 20/03/84 |
| | | NL-A- 8320239 | 01/06/84 |
| | | GB-A- 2132891 | 18/07/84 |
| | | DE-W- 3390114 | 10/01/85 |

For more details about this annex :
see Official Journal of the European Patent Office, No. 12/82